Figure 1

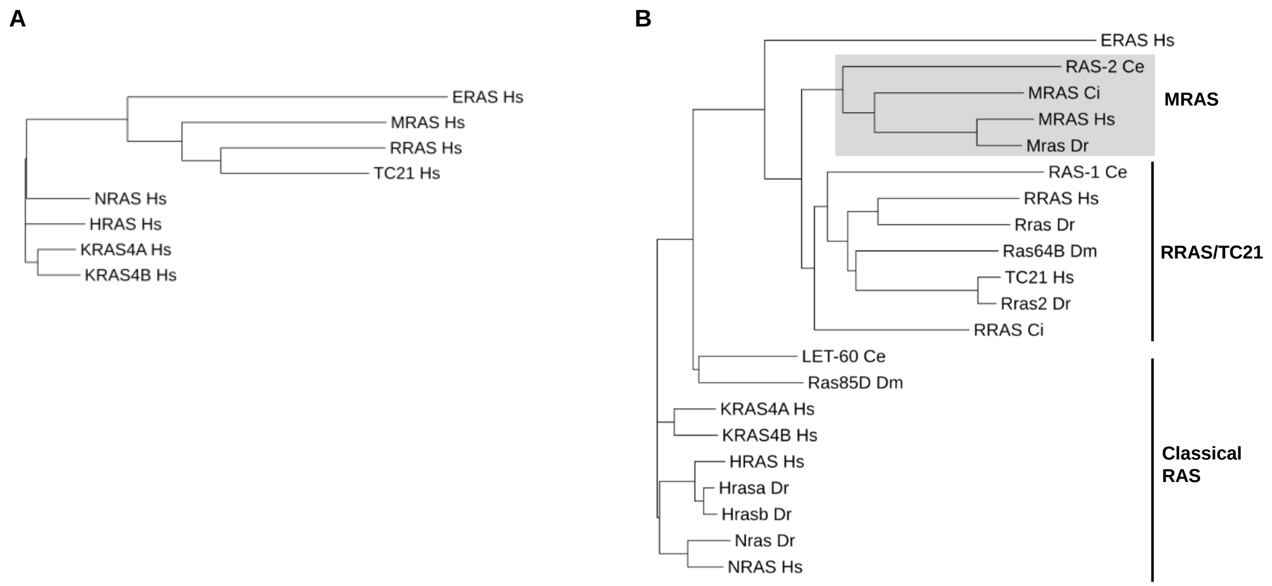


Figure 1

(A) Phylogenetic relationship of human RAS family proteins.
(B) Phylogenetic analysis of RAS family proteins in human (Hs), zebrafish (Dr), Fruitfly (Dm), nematode (Ce) and ascidian *C. intestinalis* (Ci). Sequence alignment was performed using MUSCLE (ebi.ac.uk/Tools/msa/muscle/) and tree generation with iTOL (itol.embl.de).

Figure 2

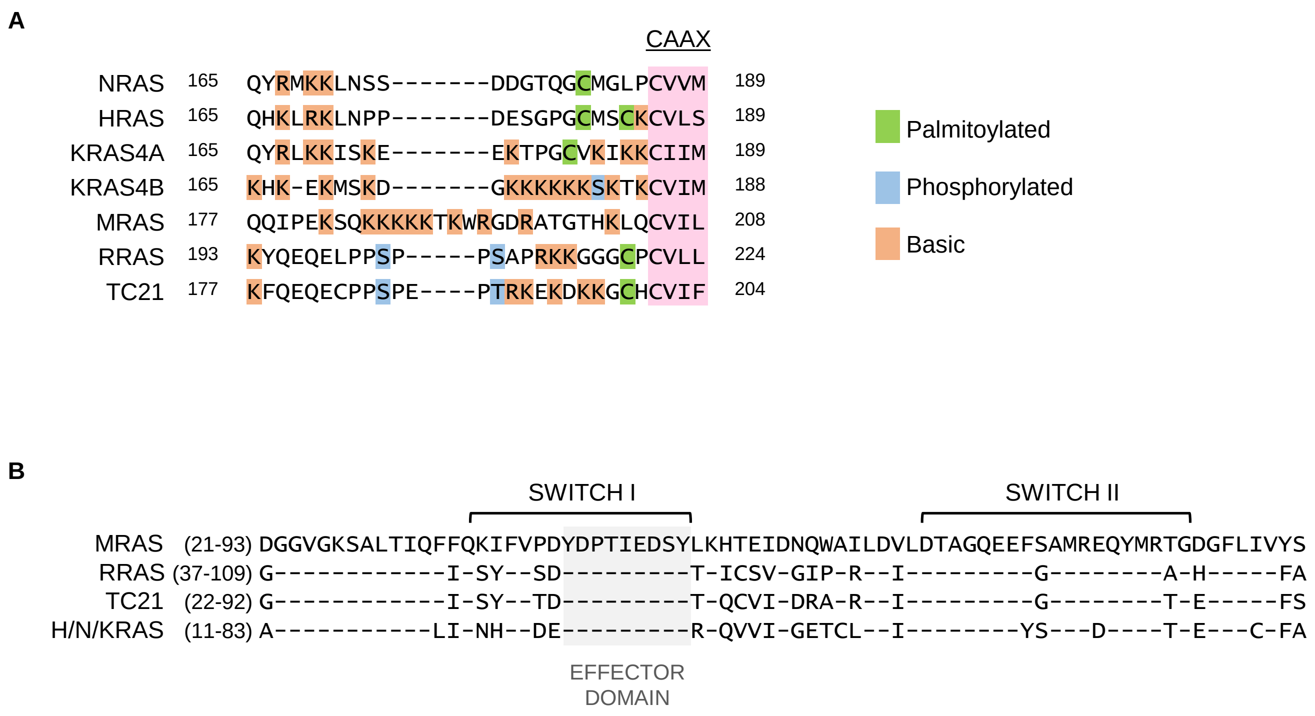


Figure 2

(A) Alignment of RAS protein hypervariable regions with features shaded according to property.
(B) Sequence alignment (of switch I and II containing regions) of MRAS with H/N/KRAS, RRAS and TC21.

Figure 3

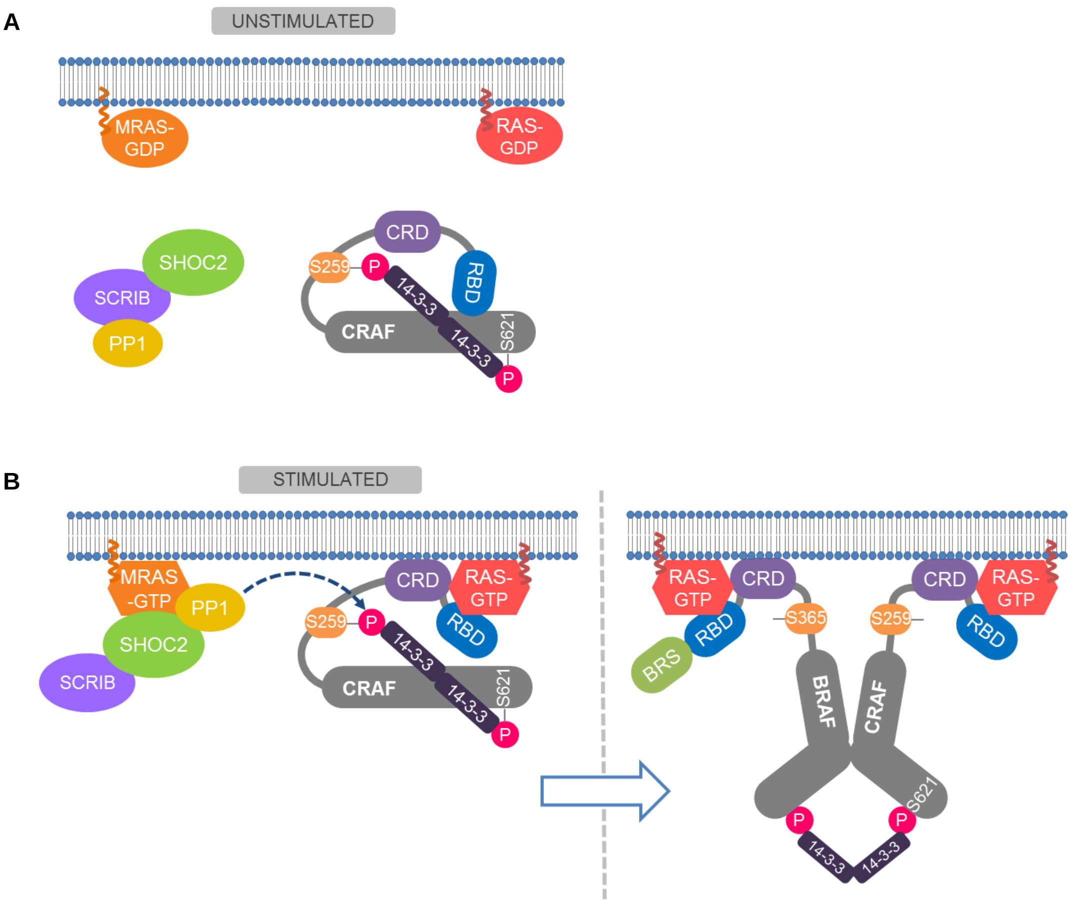


Figure 3

Coordinate inputs from RAS and MRAS-SHOC2-PP1 are required for effective RAF activation.

(A) Under basal conditions, where RAS and MRAS are GDP-bound and inactive, SHOC2 interacts with PP1 via SCRIB. BRAF and CRAF exist as auto-inhibited monomers, which are phosphorylated at S259.

(B) After pathway stimulation by a mitogen such as EGF, GTP-bound RAS recruits BRAF/CRAF to the membrane, and SHOC2 forms a complex with MRAS-GTP and PP1. Here, the complex dephosphorylates the S259/S365 site on RAF and the 14-3-3 dimer can now mediate RAF dimerization (shown here as a heterodimer of BRAF and CRAF). RBD = RAS binding domain, CRD = Cysteine rich domain, BRS = BRAF-specific region.

Figure 4

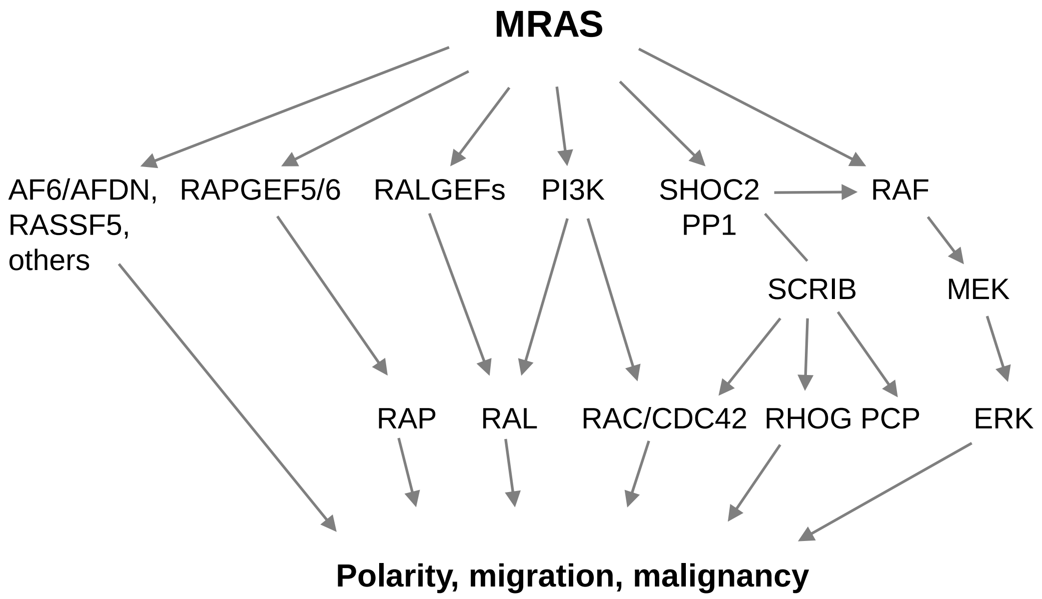
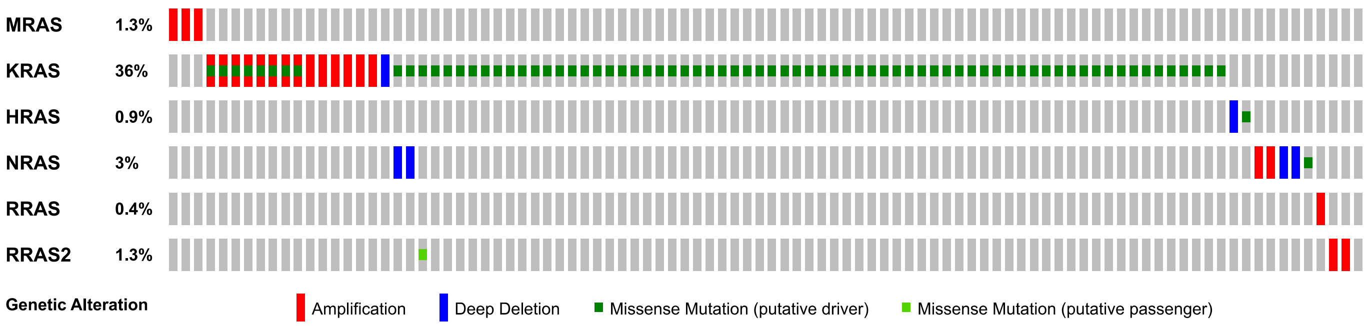


Figure 4

MRAS regulates cell polarity and migration through coordination of multiple signalling pathways. See text for details.

Figure 5

Lung Adenocarcinoma (TCGA, Provisional)



Lung Squamous Cell Carcinoma (TCGA, Provisional)

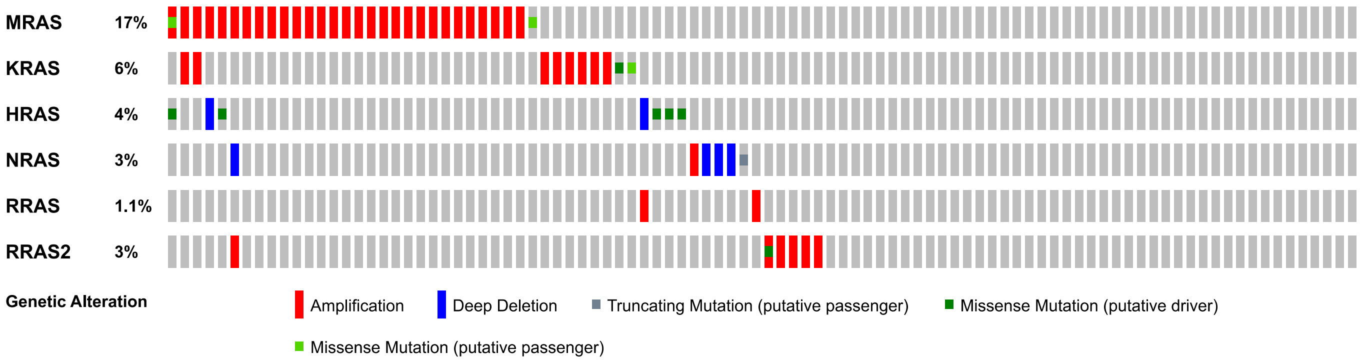


Figure 5

cBioportal oncoprints depicting genetic alterations in the classical RAS and RRAS subgroups of the RAS family of GTPases.

Figure 6

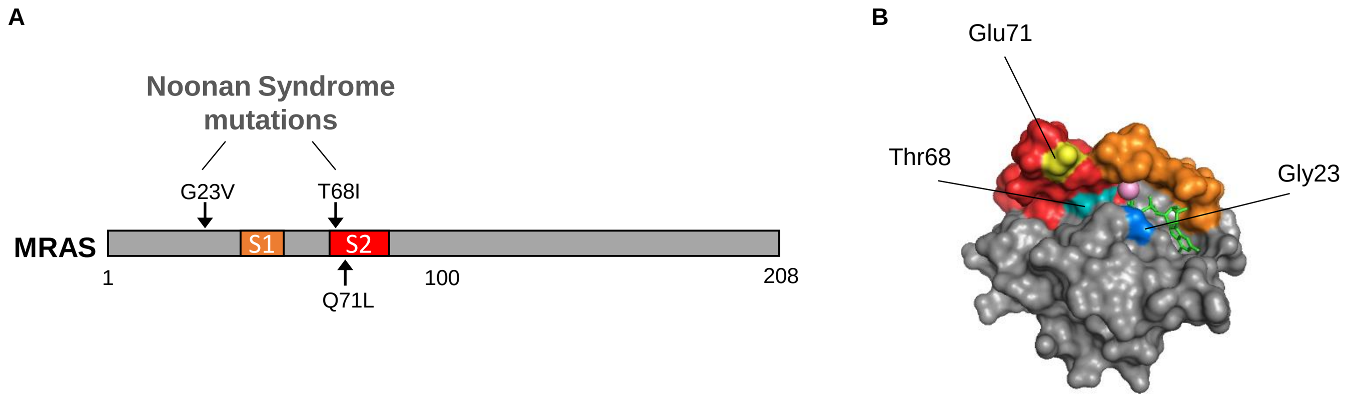


Figure 6

(A) Position of Noonan syndrome mutations (upper) and activating mutation equivalent to codon 61 in RAS (lower).
(B) Structure of MRAS bound to GDP (green sticks) (PDB 1X1R). Switch I (orange), Switch II (red) and Mg2+ (pink sphere) are shown, as well as positions of key residues Gly23 (blue), Thr68 (turquoise) and Glu71 (yellow).